FORM PTO 1390 (REV 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NUMBER: 2001_1881A

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) NEW: 10/019263

International Application No.	International Filing Date	Priority Date Claimed
PCT/JP00/04286	June 28, 2000	June 30, 1999

Title of Invention
MEDICINAL COMPOSITIONS FOR PREVENTING OR TREATING VIRAL MYOCARDITIS

Applicant(s) For DO/EO/US
Akira MATSUMORI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.

2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.

3. [] This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [X] A translation of the International Application into English (35 U.S.C. §371(c)(2)). **ATTACHMENT A**

7. [] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [] have not been made and will not be made.

8. [] A translation of the amendments to the claims under PCT Article 19.

9. [X] An executed oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). **ATTACHMENT B**

10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**

12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

ATTACHMENT D

13. [X] A FIRST preliminary amendment. **ATTACHMENT E**

[] A SECOND or SUBSEQUENT preliminary amendment.

14. [] Other items or information:

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEE FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975.

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) NEW 10/019263	INTERNATIONAL APPLICATION NO. PCT/JP00/04286	ATTORNEY'S DOCKET NO. 2001_1881A

15. [X] The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00		
International Search Report has been prepared by the EPO or JPO ..... $ 890.00		
International preliminary examination fee not paid to USPTO but international search paid to USPTO ..... $ 740.00		
International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $ 690.00		
International preliminary examination fee paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate	
Total Claims	-20 =		X $18.00	$
Independent Claims	6 - 3 =	3	X $84.00	$252.00
Multiple dependent claim(s) (if applicable)			+ $280.00	$
TOTAL OF ABOVE CALCULATIONS =				$1,142.00
[] Small Entity Status is hereby asserted. Above fees are reduced by 1/2.				$
SUBTOTAL =				$1,142.00
Processing fee of $130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$1,142.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property +				$40.00
TOTAL FEES ENCLOSED =				$1,182.00
			Amount to be refunded	$
			Amount to be charged	$

a. [X] A check in the amount of $1,182.00 to cover the above fees is enclosed. A duplicate copy of this form is enclosed.

b. [] Please charge my Deposit Account No. 23-0975 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

19. CORRESPONDENCE ADDRESS

000513

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December 28, 2001

[CHECK NO. 48144]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Akira MATSUMORI : **Attn: BOX PCT**

Serial No. NEW : **Docket No. 2001_1881A**

Filed December 28, 2001 :

MEDICINAL COMPOSITIONS FOR PREVENTING
OR TREATING VIRAL MYOCARDITIS
[Corresponding to PCT/JP00/04286
Filed June 28, 2000]

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents,
Washington, DC 20231

Sir:

Prior to calculating the filing fee, please amend the above-identified application as follows:

IN THE SPECIFICATION

Page 1, immediately after the title, please insert:

This application is a 371 of PCT/JP00/04286 filed June 28, 2000.

IN THE CLAIMS

Cancel without prejudice claims 1-24.

Please add the following new claims:

25. **(New)** A method for the prophylaxis or treatment of viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof to a patient in need thereof.

26. **(New)** A method for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof to a patient in need thereof.

27. **(New)** The method of claim 25, wherein the viral myocarditis is caused by RNA virus or hepatitis virus.

28. **(New)** The method of claim 27, wherein the RNA virus is orthomyxovirus or picornavirus.

29. **(New)** The method of claim 26, wherein the viral disease is viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis or viral pericarditis.

30. **(New)** A method for the amelioration or prophylaxis of viral cytotoxicity, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof to a patient in need thereof.

31. **(New)** The method of claim 26, wherein the viral diseases induced by viral myocarditis are caused by RNA virus or hepatitis virus.

32. **(New)** The method of claim 31, wherein the RNA virus is orthomyxovirus or picornavirus.

33. **(New)** A method for the prophylaxis or treatment of viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride to a patient in need thereof.

34. **(New)** A method for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride to a patient in need thereof.

35. **(New)** A method for the amelioration of prophylaxis of viral cytotoxicity, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride to a patient in need thereof.

REMARKS

The specification has been amended to reflect the 371 status.

In addition, claims 1-24 of the international application as originally filed have been cancelled without prejudice and new claims 25-35 are added. The new claims are supported by original claims 7-11 in the specification at page 9, lines 24-25.

Attached hereto is a marked-up version of the changes to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

Favorable action on the merits is solicited.

Respectfully submitted,

Akira MATSUMORI

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December 28, 2001

SPECIFICATION

MEDICINAL COMPOSITIONS FOR PREVENTING OR TREATING VIRAL MYOCARDITIS

This application is a 371 of PCT/JP00/04280 Filed June 28, 2000.

Technical Field

The present invention relates to a pharmaceutical composition for the prophylaxis and treatment of viral myocarditis or viral diseases induced by viral myocarditis, which composition comprises 2-amino-2-(2-(4-octylphenyl)-ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof as an active ingredient. More particularly, the present invention relates to a pharmaceutical composition for the amelioration and prophylaxis of viral cytotoxicity. The present invention also relates to a method for the prophylaxis or treatment of viral myocarditis or viral diseases induced by viral myocarditis, which method comprises administering 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof. The present invention further relates to use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the prophylaxis and treatment of viral myocarditis or viral diseases induced by viral myocarditis.

Background Art

Conventionally, viral diseases have been mainly prevented by the use of virus vaccines. However, vaccines are made specifically for individual viruses and are effective only for such individual viruses. There are numerous kinds of viruses, whereas vaccines are currently put to use against a very limited number of viruses. Moreover, viruses often include many mutant strains, but a vaccine effective against one virus often may not be so against a different virus of the same kind. In addition, it is extremely difficult to develop many vaccines associated with fewer side effects.

On the other hand, various antiviral agents (acyclovir,

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Background Art

Conventionally, viral diseases have been mainly prevented by the use of virus vaccines. However, vaccines are made specifically for individual viruses and are effective only for such individual viruses. There are numerous kinds of viruses, whereas vaccines are currently put to use against a very limited number of viruses. Moreover, viruses often include many mutant strains, but a vaccine effective against one virus often may not be so against a different virus of the same kind. In addition, it is extremely difficult to develop many vaccines associated with fewer side effects.

On the other hand, various antiviral agents (acyclovir,

ATTACHMENT A

ganciclovir, Ara-A etc.) have been developed and put to use, but they are effective against an extremely narrow range of viral infections, and there has been found no drug effective against a broad range of viral diseases. These antiviral agents show strong side effects, which prevents general application thereof in clinical situations. In recent years, interferon has been applied to the treatment of viral hepatitis and the like, but side effects, such as fever, occur frequently. While interferon inhibits growth of viruses, there have been found no reports on the direct prevention of cytotoxicity. Gamma globulin has been widely used for the treatment of viral diseases, but its achievement is not necessarily consistent.

2-Aminopropane-1,3-diol compounds including 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride are known as a suppressant of rejection in organ or bone marrow transplantation, and as a therapeutic agent of various autoimmune diseases (e.g., psoriasis, Behcet's disease) and rheumatic diseases (WO94/08943).

However, the prior art has never acknowledged effectiveness of a 2-aminopropane-1,3-diol compound for the treatment of viral diseases.

Disclosure of the Invention

As mentioned above, there are numerous kinds of viruses and a specific treatment against each virus is not feasible. Therefore, the prophylaxis and treatment of cytotoxicity in various organs, that occurs in many viral diseases, is extremely significant. The cytotoxicity in viral diseases is considered to be caused by direct injury due to the growth of viruses and various immunoreactions induced by viral infections. The present invention aims at the prophylaxis and treatment, irrespective of the kind of virus, of viral myocarditis and viral diseases induced by viral myocarditis, by the treatment and prevention of the onset of cytotoxicity in various organs.

The present inventor has conducted intensive studies of

a pharmaceutical agent for the prophylaxis and treatment of viral myocarditis and viral diseases induced by viral myocarditis, in an attempt to solve the above-mentioned problems, and surprisingly found that 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol and a pharmacologically acceptable salt thereof are effective, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) A pharmaceutical composition for the prophylaxis or treatment of viral myocarditis, which contains 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(2) A pharmaceutical composition for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which contains 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(3) A pharmaceutical composition for the amelioration or prophylaxis of viral cytotoxicity, which contains 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(4) A method for the prophylaxis or treatment of viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

(5) A method for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

(6) A method for the amelioration or prophylaxis of viral cytotoxicity, which comprises administering an effective amount

of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

(7) Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the prophylaxis or treatment of viral myocarditis.

(8) Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the prophylaxis or treatment of viral diseases induced by viral myocarditis.

(9) Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the amelioration or prophylaxis of viral cytotoxicity.

(10) A commercial package comprising the pharmaceutical composition of (1) and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis or treatment of viral myocarditis.

(11) A commercial package comprising the pharmaceutical composition of (2) and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis or treatment of viral diseases induced by viral myocarditis.

(12) A commercial package comprising the pharmaceutical composition of (3) and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the amelioration or prophylaxis of viral cytotoxicity.

In the present invention, viral myocarditis and viral diseases induced by viral myocarditis are preferably those induced by RNA virus or hepatitis virus. In the context of the present invention, the above-mentioned RNA virus is preferably orthomyxovirus or picornavirus. According to the present

invention, the aforementioned viral diseases are preferably viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis and viral pericarditis.

Brief Description of the Drawings

Fig. 1 shows survival rates in Experimental Example 2, wherein -■- shows a control group , -●- shows a CsA group, and -O- shows a compound 1 group.

Fig. 2 is a graph showing the cellular infiltration score in Experimental Example 2.

Fig. 3 is a graph showing the myocardial cell necrosis score in Experimental Example 2.

Fig. 4 is a graph showing the intracardiac virus titer in Experimental Example 2.

Fig. 5 is a graph showing the results of the intracardiac cytokine assay of IL-2 in Experimental Example 2.

Fig. 6 is a graph showing the results of the intracardiac cytokine assay of IL-12 in Experimental Example 2.

Fig. 7 is a graph showing the results of the intracardiac cytokine assay of IFN-γ in Experimental Example 2.

Fig. 8 is a graph showing the results of the intracardiac cytokine assay of TNF-α in Experimental Example 2.

Fig. 9 is a graph showing the results of the intracardiac NO assay in Experimental Example 2.

Detailed Description of the Invention

The 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol in the present invention is a known compound and can be produced by, for example, a method disclosed in WO94/08943.

The 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol can be converted to a pharmacologically acceptable salt, such as salts with the following acids, by treating with an acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid,

maleic acid, fumaric acid, benzoic acid, citric acid, oxalic acid, succinic acid, tartaric acid, malic acid, mandelic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and the like) in, where necessary, a suitable solvent such as water, methanol, ethanol, diethyl ether, tetrahydrofuran, dioxane and the like.

In the present invention, 2-amino-2-(2-(4-octylphenyl)-ethyl)propane-1,3-diol and a pharmacologically acceptable salt thereof are low toxic and are useful as a pharmaceutical agent for the prophylaxis and treatment of viral myocarditis and viral diseases induced thereby in animals, particularly mammals (e.g., human, dog, rabbit, mouse, rat and the like). The viral myocarditis and viral diseases induced thereby to be the target in the present invention include the diseases caused by pathogenic viruses belonging to DNA virus or RNA virus. Such pathogenic virus is exemplified in the following.

DNA virus: poxvirus, herpesvirus (herpes simplex virus, cytomegalovirus, EB virus etc), adenovirus, parvovirus

RNA virus: reovirus, togavirus, coronavirus, rhabdovirus, paramyxovirus, orthomyxovirus, bunyavirus, arenavirus, retrovirus, picornavirus, calicivirus

In particular, the pharmaceutical agent of the present invention can be preferably applied to the treatment and prophylaxis of viral myocarditis caused by the RNA virus or hepatitis virus and viral diseases induced thereby. As used herein, examples of the RNA virus include orthomyxovirus and picornavirus.

The viral diseases induced by viral myocarditis are specifically exemplified by viral hepatitis (type A, type B, type C, type E, type G, type TTV), adenovirus infection, influenza, viral pneumonia, viral bronchitis, herpes infection (herpes simplex, EB virus (infectious mononucleosis, herpes zoster), poliomyelitis, AIDS (HIV infection), adult T cell leukemia (ATL), papilloma, measles, rubella, roseola infantum,

erythema infectiosum, viral encephalitis, viral meningitis, cytomegalovirus infection, epidemic parotitis, chickenpox, rabies, viral enteritis, viral pericarditis, coxsackievirus infection, echovirus infection, hemorrhagic fever with renal syndrome, Lassa fever and the like.

Of the viral diseases mentioned above, the present invention can be preferably applied to viral hepatitis (type A, type B, type C, type E, type G, type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis and viral pericarditis.

2-Amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol and a pharmacologically acceptable salt thereof can be used orally or parenterally by inhalation, rectal administration or local administration as a pharmaceutical product composition or a preparation (e.g., powder, granule, tablet, pill, capsule, injection, syrup, emulsion, elixir, suspension, solution and the like). 2-Amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol and a pharmacologically acceptable salt thereof of the present invention may be used alone or by admixing with a pharmaceutically acceptable carrier (adjuvant, excipient, vehicle and/or diluent and the like). The pharmaceutical composition can be formulated into a preparation according to a conventional method.

In the present specification, by parenterally is meant subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, infusion and the like. A preparation for injection, such as sterile aqueous suspension or oily suspension for injection, can be prepared using a suitable dispersing agent, moistening agent or suspending agent according to a method known in the pertinent field. The sterile preparation for injection may be a sterile and injectable solution or suspension in a parenterally administrable diluent or solvent, such as aqueous solution and

the like, which is acceptable for the formulation of preparations. The usable vehicle or solvent may be, for example, water, Ringer solution, isotonic saline and the like. In addition, sterile non-volatile oil can be used as a solvent or suspending medium. Any non-volatile oil, fatty acid, natural or synthetic or semi-synthetic fatty oil or fatty acid, natural or synthetic or semi-synthetic mono-, di- or triglyceride for this end is encompassed.

The suppository for rectal administration can be produced by admixing the drug and a suitable less irritant vehicle, such as cacao butter and polyethylene glycol, which is solid at normal temperature but liquid at the temperature of intestine, and which melts in the rectum to release the drug, and the like.

The solid dosage form for oral administration may be the above-mentioned powder, granule, tablet, pill, capsule and the like. In such a dosage form, the active ingredient compound can be mixed with at least one additive, such as sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starches, agar, alginate, chitin, chitosan, pectin, tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semi-synthetic polymer or glyceride. Such dosage form may contain a different additive as does a typical dosage form. The different additive includes, for example, inert diluent, lubricant such as magnesium stearate and the like, preservative such as parahydroxybenzoate, sorbic acid and the like, antioxidant such as ascorbic acid, α-tocopherol, cysteine and the like, disintegrant, binder, thickener, buffer, sweetener, flavor, perfume and the like. The tablet and pill may be enteric coated.

The liquid for oral administration may be, for example, pharmaceutically acceptable syrup, emulsion, elixir, suspension, solution and the like. These may contain an inert diluent typically used in the pertinent field, such as water.

The dose for a specific patient is determined according to age, body weight, general health state, sex, diet, administration time, administration method, clearance rate, combination of drugs, the condition for which the patient is undergoing treatment, and other factors. 2-Amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol and a pharmacologically acceptable salt thereof are low toxic and can be used safely. While the daily dose of the compound varies depending on the condition and body weight of the patient, administration route and the like, when it is orally administered as a pharmaceutical agent for the treatment of viral myocarditis or viral diseases induced by viral myocarditis in adult, the daily dose is approximately 0.01 - 150 mg, preferably 0.1 - 100 mg, and approximately 0.01 - 50 mg, preferably 0.01 - 20 mg, by intravenous injection, which is preferably administered in one, two or three doses.

Examples

The effect of the present invention is clarified in the following by referring to Experimental Examples. These examples are for mere exemplification and the present invention is not limited in any way by these examples.

Experimental Example 1

Effect on viral myocarditis

Compound 1: 2-Amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride

(1) survival rate

Method

Four-week-old DBA/2 mice were divided into 3 groups, and EMC (Encephalomyocarditis) virus (10 pfu) was intraperitoneally inoculated. After inoculation, distilled water (solvent, group A, n=11) as a control, compound 1 (1 mg/kg/day, group B, n=10), and compound 1 (3 mg/kg/day, group C, n=10) were orally administered forcibly for 14 consecutive days using a probe. The survival rate of each group after 14 days was compared by

Kaplan-Meier method.

Results

The mice in the control group (group A, n=11) all died by day 8 (survival rate 0%) but the survival rate of the compound 1 administration group at day 14 was one mouse for group B (n=10, survival rate 10%), and 3 mice for group C (n=10, survival rate 30%). In the 3 mg/kg/day group, a statistically significant improvement in the survival rate was observed ($p<0.05$).

(2) Histopathological observation of the heart

Method

Four-week-old DBA/2 mice were divided into 3 groups and EMC (Encephalomyocarditis) virus (10 pfu) was intraperitoneally inoculated. After inoculation, distilled water (solvent, n=9) as a control, compound 1 (3 mg/kg/day, n=8), and compound 1 (10 mg/kg/day, n=8) were orally administered forcibly for 5 consecutive days using a probe. Five days later, the heart was removed, and, after fixing with formalin, subjected to hematoxylin-eosin staining, based on which heart necrosis and cellular infiltration were scored as follows.

0; no lesion,

1+; lesion in 25% or less of the heart,

2+; lesion in more than 25% and not more than 50% of the heart

3+; lesion in more than 50% and not more than 75% of the heart

4+; lesion in more than 75% and not more than 100% of the heart

Results

The results of the histopathological observation of the heart are shown in Table 1.

Table 1

	necrosis of myocardial cell	cellular infiltration*
control group	1.9±0.2	2.0±0.2
3 mg/kg/day administration group	1.7±0.4	1.6±0.2
10 mg/kg/day administration group	1.0±0.2*	1.1±0.2*

mean±SEM, *p<0.05 (vs. control group)

From Table 1, it is evident that the myocardial cell necrosis and cellular infiltration of the heart were improved dose dependently in the 10 mg/kg/day administration group at 5 days after the EMC virus inoculation.

From the above results, 2-amino-2-(2-(4-octylphenyl)-ethyl)propane-1,3-diol hydrochloride was found to improve the mortality rate of the mice by EMC viral infection, ameliorate viral myocarditis and prove effective against viral infection.

The animal model of the above-mentioned dilated cardiomyopathy is described in Circulation. 65:1230-1235, 1982 and Circulation. 66:355-360, 1982.

Experimental Example 2

The effects on viral myocarditis of compound 1 and an immunosuppressant, cyclosporin A (hereinafter to be referred to as CsA), were compared. The compound 1 was dissolved in sterile distilled water and administered, and CsA was dissolved in olive oil and administered.

(1) Survival rate

Method

Four-week-old DBA/2 male mice were divided into 3 groups, and EMC virus (10 pfu) was intraperitoneally inoculated. After inoculation, distilled water (solvent, control group, n=21), CsA (40 mg/kg/day, CsA group, n=9), and compound 1 (10 mg/kg/day, compound 1 group, n=22) were orally administered forcibly for 14 consecutive days using a probe. The survival

rate of each group after 14 days was compared by Kaplan-Meier method.

Results

The results are shown in Fig. 1. The mice in the control group (-■-) all died by day 10 (survival rate 0%). The mice in the CsA group (-●-) all died by day 7, and the survival rate dropped significantly as compared to the control group. In contrast, the survival rate of the compound 1 group (-O-) at day 14 was 27% (6 out of 22 survived). A significant difference was found in the survival rates between the CsA group and the control group (*$p<0.05$).

(2) Histopathological observation of the heart

Method

Four-week-old male DBA/2 mice were divided into 3 groups and EMC virus (10 pfu) was intraperitoneally inoculated. After inoculation, distilled water (solvent, n=9) as a control, CsA (40 mg/kg/day, n=6), and compound 1 (10 mg/kg/day, n=8) were orally administered forcibly for 5 consecutive days using a probe. Five days later, the heart was harvested, and, after fixing with formalin, subjected to hematoxylin-eosin staining, based on which heart necrosis and cellular infiltration were scored according to the criteria shown in Experimental Example 1.

The myocardial cell necrosis and cellular infiltration were independently scored by two observers and averaged. The statistical analysis was performed by one way analysis of variance (ANOVA) and Fisher's protected least significant difference test.

Results

The results are shown in Fig. 2 (cellular infiltration), Fig. 3 (necrosis of myocardial cell) and Table 2.

Table 2

	cellular infiltration	necrosis of myocardial cell
control group	2.00±0.19	1.89±0.23
CsA group	1.50±0.26(NS)	2.00±0.32(NS)
compound 1 group	1.06±0.19**	1.00±0.19*

mean±SEM, NS: no significant difference, **p<0.01, *p<0.05 (vs. control group)

While the score of cellular infiltration in the CsA group was lower than that of the control group, no significant difference was found. While the score of myocardial cell necrosis in the CsA group was slightly higher than that of the control group, no significant difference was found. In contrast, the scores of both cellular infiltration and myocardial cell necrosis were significantly lower in the compound 1 group than in the control group. Therefore, a significant ameliorating effect on myocardial cell necrosis and cellular infiltration was found by the administration of compound 1.

(3) Intracardiac virus titer

Method

Four-week-old male DBA/2 mice were divided into 3 groups and EMC virus (10 pfu) was intraperitoneally inoculated. After inoculation, distilled water (solvent, n=8) as a control, CsA (40 mg/kg/day, n=5), and compound 1 (10 mg/kg/day, n=7) were orally administered forcibly for 5 consecutive days using a probe. Five days later, the heart was aseptically harvested from the mice, and after weighing the ventricle, homogenized in phosphate-buffered saline (PBS, 1 ml). The homogenate was centrifuged at 4°C, 1,500 g for 15 min and the supernatant (0.1 ml) was inoculated to human amnion FL cell monolayer and cultured at 37°C for 60 min in 5% CO_2. The cells were overlaid

with a medium (3 ml) containing 4% fetal calf serum and 1% methylcellulose. After culture under 5% CO_2-containing humidified atmosphere at 37°C for 20 hr, the cells were fixed with acetic acid-methanol (1:2) and stained with 1% crystal violet. The plaques were counted under an inverted microscope (Circulation. 89:846-851, 1994). When the plaques are too many to count, the supernatant is appropriately diluted with Dulbecco's modified Eagle's medium (DMEM) and subjected to a similar assay. The test was repeated and the mean was taken. The virus titer was expressed in pfu/g heart. The statistical analysis was conducted by one way ANOVA and Fisher's protected least significant difference test.

Results

The results are shown in Fig. 4 and Table 3.

Table 3

	virus titer (pfu/g heart)
control group	$5.18\pm2.73 \times 10^6$
CsA group	$9.94\pm6.30 \times 10^7$ *
compound 1 group	$1.23\pm0.53 \times 10^7$ (NS)

mean±SEM, NS: no significant difference, *$p<0.05$ (vs. control group)

CsA increased virus replication in the heart by about 20 times as compared to the control group. In contrast, compound 1 showed no effect of increase in virus replication, unlike CsA.

(4) Intracardiac cytokine assay

Method

The ventricle of the mice, harvested in the above-mentioned (3) at day 5, was homogenized in PBS (1 ml) using an ultrasonic homogenizer and centrifuged at 4°C, 14,000 rpm for 20 min. The supernatant was used as the samples for the IL-2,

IL-12, IFN-γ and TNF-α assay. The protein concentration of each cytokine was assayed by ELISA using a commercially available kit (Circulation. 100:1102-1108, 1999). The ELISA kits for the mouse IL-2 and IFN-γ were purchased from GENZYME Corporation, Cambridge, U.S.A. and the ELISA kits for mouse IL-12 and TNF-α were purchased from ENDOGEN Inc., Cambridge, U.S.A.

The total protein concentration of each supernatant was measured by bicinchoninic acid (BCA) method, and the ratio of the cytokine concentration to the total protein concentration was calculated (J. Am. Coll. Cardiol. 33:1400-1407, 1999). Each cytokine protein concentration was expressed in pg/mg total protein or ng/mg total protein. The statistical analysis was conducted by one way ANOVA and Fisher's protected least significant difference test.

Results

The results are shown in Figs. 5 - 8 and Table 4.

Table 4

	IL-2 (ng/mg total protein)	IL-12 (pg/mg total protein)	IFN-γ (pg/mg total protein)	TNF-α (ng/mg total protein)
control group	12.79±1.24	71.76± 7.37	151.20±15.66	4.11±0.11
CsA group	3.91±0.31#	15.75±4.67#	59.15± 9.41#	4.73±0.17*
compound 1 group	6.06±0.67#	46.00±12.82*	108.86±12.98*	3.72±0.25**

mean±SEM, #p<0.001 (vs. control group)

*p<0.05 (vs. control group)

**p<0.01 (vs. CsA group)

The IL-2 concentration known to relate to T cell proliferation was suppressed in both the CsA group and compound 1 group. However, the degree of IL-2 suppression in the compound 1 group was lower than that in the CsA group. The

concentration of IFN-γ capable of inhibiting virus replication (Jpn. Circ. J. 51:661-664, 1987) was markedly reduced in the CsA group, but reduced by a smaller degree in the compound 1 group. Similarly, the concentration of Th1 (1 type helper T cell)-specific cytokine IL-12 was markedly reduced in the CsA group, but less so in the compound 1 group. Conversely, one of the inflammatory cytokines, TNF-α, showed an increase in the concentration in the CsA group as compared to the control group, but no effect was found in the compound 1 group.

(5) Intracardiac nitric oxide (NO) assay

The intracardiac NO content was measured using the same supernatant as used for the cytokine assay according to a modified method of Griess method (J. Am. Coll. Cardiol. 33:1400-1407, 1999; Anal. Biochem. 224:502-508, 1995). In brief, the supernatant or standard nitrite (50 μl) was mixed with 10 μM βNADPH (10 μl). Thereto was added a master mix previously mixed (500 μM glucose-6-phosphate, 160 U/l glucose-6-phosphate dehydrogenase, 80 U/l nitrate reductase, 0.2 mM phosphate buffer)(40 μl), and the mixture was incubated at 20°C for 45 min. 1% Sulfanilamide (50 μl) in 5% H_3PO_4 and 0.1% naphthylethylenediamine dihydrochloride (50 μl) were further added, and the mixture was incubated at 20°C for 10 min. Optical density at 540 nm was measured using a microplate reader. The nitrite concentration of each sample was calculated based on the standard product. The measurement of each sample and the standard product was done in duplicate. The intracardiac NO content was determined by dividing each nitrite concentration by the total protein concentration of each supernatant and expressed in μM/mg total protein. The statistical analysis was conducted by one way ANOVA and Fisher's protected least significant difference test.

Results

The results are shown in Fig. 9 and Table 5.

Table 5

	NO content (μM/mg total protein)
control group	2.07±0.20#
CsA group	4.56±0.68
compound 1 group	1.91±0.34#

mean±SEM, #p<0.001 (vs. CsA group)

The CsA group showed a significant increase in the intracardiac NO content as compared to the control group, but the compound 1 group showed no significant difference from the control group.

To sum up the above-mentioned results, the expression of IL-2, IL-12 and IFN-γ in the heart was suppressed in both the compound 1 group and the CsA group as compared to the control group, but the level of suppression was low in the compound 1 group. TNF-α and NO increased significantly in the CsA group, but the compound 1 group showed no significant difference from the control group. IL-2 is involved in the T cell proliferation and has an activity to induce production of IFN-γ from T cell and NK cell. A Th1 specific cytokine, IL-12, induces production of IFN-γ from T cell and NK cell. IFN-γ shows a virus growth inhibitory activity by the activation of macrophage. Thus, the above-mentioned results revealing that the level of inhibition of the production of IL-2, IL-12 and IFN-γ is higher in the CsA group than in the compound 1 group is in line with the results of the above-mentioned (3) wherein CsA increased virus replication but the compound 1 did not have such effect. In addition, an inflammatory cytokine, TNF-α, has a cytotoxic activity and NO is known to cause injury of cardiac muscle. From the above-mentioned results, it was clarified that CsA increased TNF-α and NO, but compound 1 did not. Therefore, compound 1 is effective for the amelioration of the

viral cytotoxicity.

The above results reveal that compound 1 [2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol hydrochloride] is effective for the treatment of viral myocarditis, without inducing virus replication.

Immunosuppressants such as cyclosporin and the like are used for the immunotherapy after organ or bone marrow transplantation. Its use for this end is problematic in that it causes severe infection due to the virus such as cytomegalovirus and the like. From the results of the above-mentioned tests, 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol of the present invention does not have, unlike conventional immunosuppressants, an effect of virus growth induction. Therefore, it is associated with an extremely small possibility of inducing virus (e.g., cytomegalovirus) infections even during the immunotherapy after organ or bone marrow transplantation.

Formulation Example

(1) Tablet

Tablets having the following composition and containing compound 1 are produced.

compound 1	1	mg
lactose	90	mg
crystalline cellulose	25	mg
magnesium stearate	4	mg

(2) Soft capsule (per capsule)

compound 1	30	mg
polyethylene glycol 300	300	mg
polysorbate 80	20	mg

Production method

Polyethylene glycol 300 and polysorbate 80 are added to compound 1 and the mixture is filled in a soft capsule.

(3) Injection (per ampoule, 10 ml)

compound 1	0.3 %	(30 mg)
polyethylene glycol 300	20 %	(2 g)
ethanol	60 %	(6 g)

The total amount is adjusted to 10 ml with distilled water for injection.

<u>Production method</u>

Ethanol and polyethylene glycol 300 are added to compound 1 for dissolution, and distilled water for injection is added to make the total amount 10 ml, whereby an injection containing 30 mg of compound 1 per ampoule is obtained.

Industrial Applicability

According to the present invention, administration of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof is effective against cytotoxicity caused by virus, is therapeutically effective against viral myocarditis or viral diseases induced by viral myocarditis, and is also effective for the prophylaxis of these diseases.

This application is based on patent application No. 185297/1999 filed in Japan, the contents of which are hereby incorporated by reference.

WHAT IS CLAIMED IS

1. A pharmaceutical composition for the prophylaxis or treatment of viral myocarditis, which comprises 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which comprises 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

3. The pharmaceutical composition of claim 1 or claim 2, wherein the viral myocarditis and viral diseases induced by viral myocarditis are caused by RNA virus or hepatitis virus.

4. The pharmaceutical composition of claim 3, wherein the RNA virus is orthomyxovirus or picornavirus.

5. The pharmaceutical composition of claim 2, wherein the viral disease is viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis or viral pericarditis.

6. A pharmaceutical composition for the amelioration or prophylaxis of viral cytotoxicity, which comprises 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method for the prophylaxis or treatment of viral myocarditis, which comprises administering an effective amount

of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

8. A method for the prophylaxis or treatment of viral diseases induced by viral myocarditis, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

9. The method of claim 7 or claim 8, wherein the viral myocarditis and viral diseases induced by viral myocarditis are caused by RNA virus or hepatitis virus.

10. The method of claim 9, wherein the RNA virus is orthomyxovirus or picornavirus.

11. The method of claim 8, wherein the viral disease is viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis or viral pericarditis.

12. A method for the amelioration or prophylaxis of viral cytotoxicity, which comprises administering an effective amount of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof.

13. Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the prophylaxis or treatment of viral myocarditis.

14. Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the prophylaxis or

treatment of viral diseases induced by viral myocarditis.

15. The use of claim 13 or claim 14, wherein the viral myocarditis and viral diseases induced by viral myocarditis are induced by RNA virus or hepatitis virus.

16. The use of claim 15, wherein the RNA virus is orthomyxovirus or picornavirus.

17. The use of claim 14, wherein the viral disease is viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis or viral pericarditis.

18. Use of 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or a pharmacologically acceptable salt thereof for the production of a pharmaceutical agent for the amelioration or prophylaxis of viral cytotoxicity.

19. A commercial package comprising the pharmaceutical composition of claim 1 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis or treatment of viral myocarditis.

20. A commercial package comprising the pharmaceutical composition of claim 2 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the prophylaxis or treatment of viral diseases induced by viral myocarditis.

21. The commercial package of claim 19 or claim 20, wherein the viral myocarditis and viral diseases induced by viral

myocarditis are induced by RNA virus or hepatitis virus.

22. The commercial package of claim 21, wherein the RNA virus is orthomyxovirus or picornavirus.

23. The commercial package of claim 20, wherein the viral disease is viral hepatitis (type A, type B, type C, type E, type G and type TTV), adenovirus infection, influenza, herpes infection, viral encephalitis, cytomegalovirus infection, viral enteritis or viral pericarditis.

24. A commercial package comprising the pharmaceutical composition of claim 6 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for the amelioration or prophylaxis of viral cytotoxicity.

FIG. 1

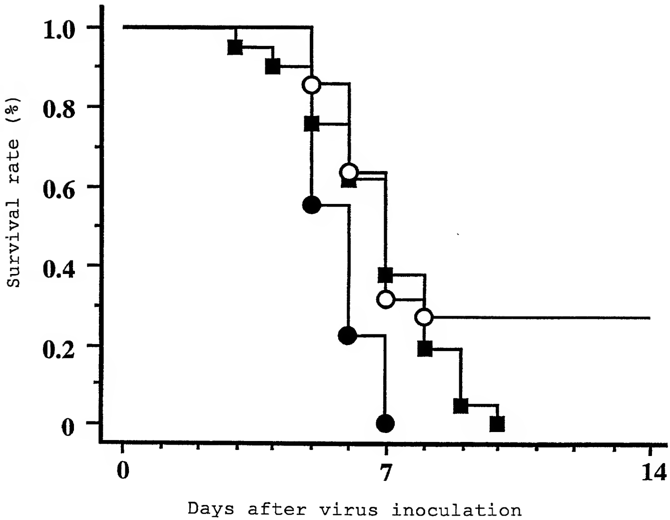


FIG. 2

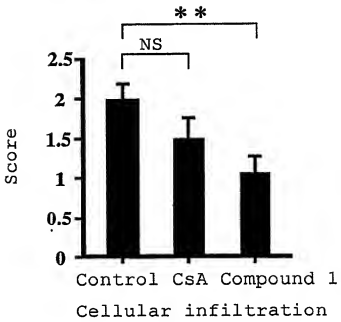


FIG. 3

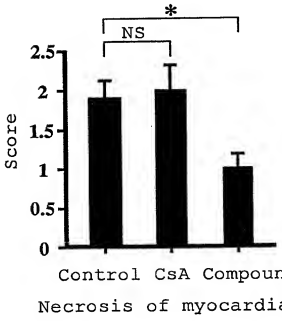


FIG. 4

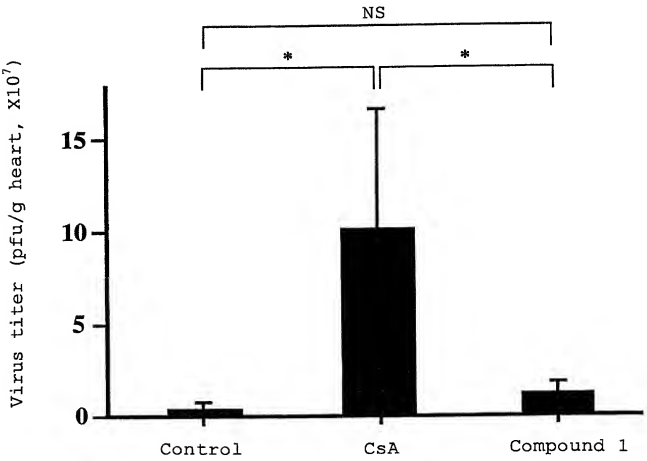


FIG. 5

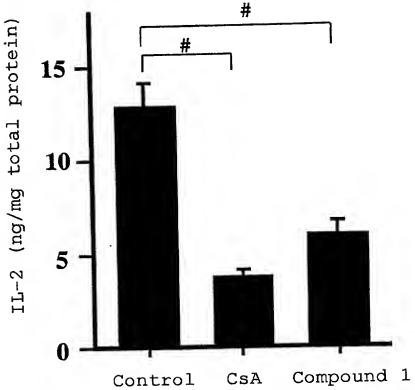


FIG. 6

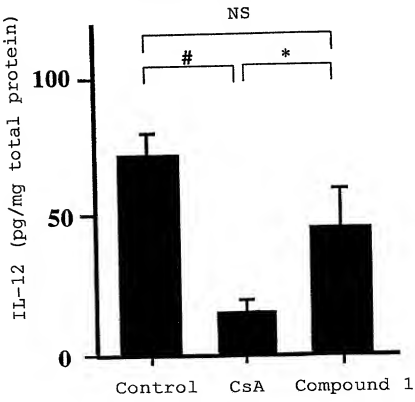


FIG. 7

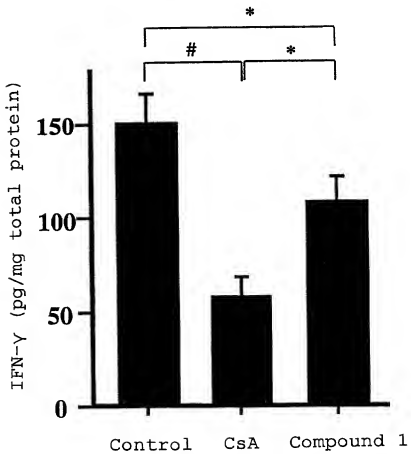


FIG. 8

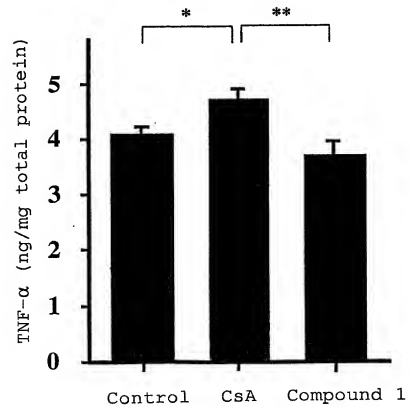
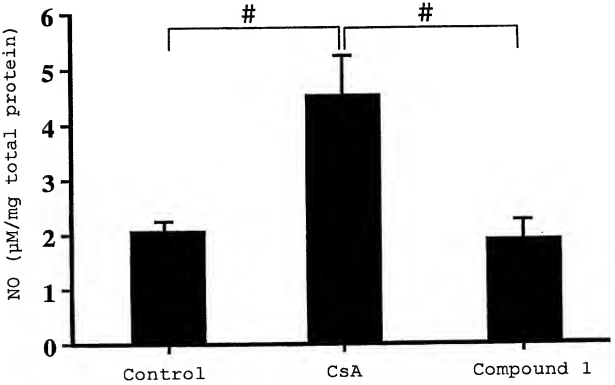


FIG. 9



DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION
米国特許出願宣言書及び委任状

Japanese Language Declaration
日本語宣言書（英語でご記入下さい）

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
下記の氏名の発明者として、私は以下の通り宣言します。私の住所、郵便物送付先、国籍は下記の私の氏名の後に記載された通りです。下記の名称の発明に関して請求の範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の氏名が複数の場合）であると信じています。

Title（発明の名称）:

MEDICINAL COMPOSITIONS FOR PREVENTING OR TREATING VIRAL MYOCARDITIS

of which is described and claimed in:
上記名称の発明を記述し特許請求する書類は、以下のいずれかです。

(X) the attached specification, or
本状に添付した明細書

( ) the specification in the application Serial No. _____ filed _____;
_____提出の米国出願番号_____で、
and with amendments through _____ (if applicable), or
(該当する場合) ___(上記日付等)___に訂正された明細書

(X) the specification in International Application No. PCT/JP00/04286, filed on June 28, 2000,
and as amended on _____ (if applicable).
___(上記日付)___提出の特許協力条約に基づく国際出願番号PCT/___(上記出願番号)___で、
(該当する場合) ___(上記日付等)___に訂正された明細書

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.
私は、特許請求の範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.
私は、連邦規則法典第37編第1条56項に定義されるとおり、特許性の有無について重要な情報を開示する義務があることを認めます。

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:
私は、米国法典第35編119条（もし本願が意匠に関する出願の場合は172条）に基き、下記の特許出願又は発明者証の出願についての優先権の利益をここに主張するとともに、優先権主張の基礎となる出願日を有する、本出願の前に出願された特許または発明者証の出願を以下にすべて、枠内をマークすることで示しています。

COUNTRY 国名	APPLICATION NO. 出願番号	DATE OF FILING 出願日	PRIORITY CLAIMED 優先権主張
Japan	185297/1999	June 30, 1999	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or 365(c) of any PCT international application designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which become available between the filing date of the prior application and the national or PCT international filing date of this application:

 ATTACHMENT B

私は、米国法典第35編120条に基いて下記の米国特許出願、又は米国を指定している特許協力条約365条(c)に基づく優先権をここに主張します。また、本出願の各請求の範囲の技術的事項が米国法典第35編112条第1段で規定された方法で先行する米国特許出願に開示されていない限り、当該先行出願の出願日以降で本出願の国内又はPCTに基づく国際出願の提出日までの期間中に入手できるようになった、連邦規則法典第37編1条56項で定義された特許性の有無に関する重要な情報について、開示義務があることを認識しています。

APPLICATION SERIAL NO. 出願番号	U.S. FILING DATE 米国出願日	STATUS: PATENTED, PENDING, ABANDONED 現状:特許許可済、係属中、放棄済

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils E. Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.
私は、本出願の審査及び本出願に関連するすべてのビジネスに関わる手続きを米国特許商標局に対して遂行するため、共同でWENDEROTH, LIND & PONACK, L.L.P.法律事務所を構成しているMichael R. Davis（登録番号第25,134号）、Matthew M. Jacob（登録番号第25,154号）、Warren M. Cheek, Jr.（登録番号第33,367号）、Nils E. Pedersen（登録番号第33,145号）、Charles R. Watts（登録番号第33,142号）及びMichael S. Huppert（登録番号第40,268号）並びにカスタマー番号第000513号に付帯する他の弁護士及び弁理士を名いたします。

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from TAKASHIMA INTERNATIONAL PATENT OFFICE as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.
私は、本願に関して米国特許商標局で行われるあらゆる手続行為に関し、ここに指名した米国弁護士を、弁護士と私との間で直接連絡をとることなく、（米国弁護士が連絡する相手先。譲受人もしくは日本の代理人等）からの指示を受けそれに従うことを、ここに承認します。指示を送る者が変更される場合は、その旨を上記米国弁護士は私から告知されます。

Direct Correspondence to Customer No:（カスタマー番号）	Direct Telephone Calls to:（連絡先電話番号）
000513 PATENT TRADEMARK OFFICE	WENDEROTH, LIND & PONACK, L.L.P. 2033 "K" Street, N.W., Suite 800 Washington, D.C. 20006-1021 Phone:(202) 721-8200 （電話番号） Fax:(202) 721-8250 （ファクシミリ番号）

	FAMILY NAME 姓名	FIRST GIVEN NAME 氏名	SECOND GIVEN NAME ミドルネーム等その他の氏名
Full Name of First Inventor 第一発明者の氏名	MATSUMORI	Akira	
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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

私は、私自身の知識に基づいて本宣言書中で私が行う表明が真実であり、かつ私の入手した情報と私の信じるところに基づく表明がすべて真実であると信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第18編第1001条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行えば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

1st Inventor ______________________ Date December 7, 2001
第一発明者（署名、ローマ字もしくは漢字） Akira MATSUMORI 署名の日付

The above application may be more particularly identified as follows:
上記出願は、さらに具体的には以下のように特定されます。

U.S. Application Serial No. ______________________ Filing Date ______________________
______________________提出の米国特許出願第______________________号

Applicant Reference Number ______________________ Atty Docket No. ______________________
出願人側整理番号______________________ 米国弁護士側管理番号 ______________________

Title of Invention ______________________
発明の名称